https://doi.org/10.31925/farmacia.2023.6.2 **REVIEW**

COMBINED ANTI-ANG2/TIE AND ANTI-VEGF INTRAVITREAL THERAPY IN AGE-RELATED MACULAR DEGENERATION – A SYSTEMATIC REVIEW

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Abstract

Age-related macular degeneration is a multifactorial condition, associated with the degeneration of the retinal pigment epithelium (RPE) at the macular level and subretinal neovascular membranes. The use of anti-VEGF agents has brought significant improvements in the control of the disease, but it continues to represent one of the main causes of irreversible blindness in the world's elderly population. Recently, faricimab, a new bispecific, anti-VEGF and anti-ANG2/Tie agent was approved in the therapy of neovascular age-related macular degeneration (nAMD). A systematic review was carried out on Web of Science and PubMed to document the efficiency and safety of intravitreal therapy with faricimab. After removing duplicates and applying the exclusion and inclusion criteria, 16 studies were identified, on a total of 2970 patients with nAMD, with a mean follow-up period of 24.27 ± 13.3 weeks. In naïve patients, intravitreal therapy with faricimab was comparable to anti-VEGF in terms of anatomical and functional results, but allowed spacing of injections after the loading period. In patients with suboptimal response or with a switch from anti-VEGF therapy, faricimab did not significantly improve visual acuity, but reduced retinal and/or choroidal thickness. Intravitreal faricimab is a safe and effective therapy, with prolonged control of the disease in most cases, improving the patients' quality of life.

Rezumat

Degenerescența maculară legata de vârstă este o afecțiune multifactorială, asociată cu degenerarea epiteliului pigmentar retinian (EPR) la nivel macular și formarea de membrane neovasculare subretiniene. Introducerea agenților anti-VEGF a adus îmbunătățiri semnificative în controlul bolii, dar aceasta continuă să reprezinte una din cauzele principale de orbire ireversibilă la populația în vârstă în lume. Recent, faricimab, un nou agent bispecific, anti-VEGF și anti ANG2/Tie a fost aprobat în terapia degenerescenței maculare legate de vârstă, forma neovasculară. Un review sistematic al studiilor publicate pe Web of Science și Pubmed, a fost realizat pentru a documenta eficiența și siguranța terapiei intravitreene cu faricimab. După înlăturarea duplicatelor și aplicarea criteriilor de excludere și includere, au fost identificate 16 studii, incluzând un total de 2970 pacienți, și o perioadă medie de urmărire de 24,27 ± 13,3 săptămâni. La pacienții naivi, terapia intravitreană cu faricimab a fost comparabilă cu cea anti-VEGF în ceea ce privește rezulaltatele anatomice și funcționale, dar a permis spațierea injecțiilor după perioada de încărcare. La pacienții cu răspuns suboptimal sau cu *switch* de la terapia cu anti-VEGF, faricimab nu a îmbunătățit semnificativ acuitatea vizuală, dar a redus grosimea retiniană și/sau coroidiană. Terapia intravitreană cu faricimab este eficientă și sigură, obținând un control prelungit al bolii la majoritatea cazurilor, îmbunătățind calitatea vieții pacienților.

Keywords: age related macular degeneration, anti-VEGF, anti-Ang2/Tie, choroidal neovascularization (CNV), faricimab

Introduction

Age related macular degeneration is a major cause of blindness and visual impairment in elderly worldwide, affecting more than 200 million people [1]. Due to the ascendent trends in population aging, by 2040, this number is projected to rise to close to 300 million [2]. The pathogenesis of AMD is still a subject of research, involving a complex interaction between genetic, metabolic and inflammatory factors. Degenerative changes of the retinal photoreceptors, retinal pigment

epithelium and Bruch's membrane affect irreversible the central vision. Traditionally, there are 2 forms of AMD, atrophic or non-exudative AMD and exudative or neovascular AMD (nAMD), based on the presence of choroidal neovascularization (CNV) [3].

Although substantial progress has been made with the introduction of anti-VEGF in the treatment of nAMD, there is still a significant percentage of cases that do not gain AV or in which the subretinal edema associated with the exudation also enters [4-7]. CNV remains persistent, despite compliance with the anti-VEGF administration protocol. Epidemiological studies show that after 1 year of anti-VEGF treatment, 68% of patients do not reach the visual acuity required for driving, of 0.5 or 20/40 Snellen [4]. Also, the increased frequency of repeating intravitreal injections places an increased burden on these elderly patients and their families, resulting in numerous cases in postponing or missing appointments and suboptimal therapeutic results [5, 6]. In addition to neovascularization mediated by VEGF, an important role is played by inflammation, alteration of vascular permeability and fibrosis. Experimental research has shown that the Ang/Tie pathway plays an important role in CNV pathogenesis. Under normal condition, Angiopoietin 1 bind and induce phosphorylation of Tie 2, leading to vascular stability, decrease inflammation and promoting cell survival. Angiopoietin 2 was found in increased concentrations in the vitreous of patients with nAMD, diabetic macular oedema and retinal venous obstructions. Several experimental studies showed that this cytokine has an important role both in inflammation and exudation, by competing Angiopoietin 1 in binding Ang/Tie 2 receptors, thus sensitizing blood vessels to the effects of vascular endothelial growth factor-A (VEGF-A) [7-9].

Faricimab is a novel 146 kDa monoclonal antibody that specifically and independently binds VEGF-A and Ang2 by its two distinctive Fab regions [10]. By this dual action, faricimab was associated to anti-inflammatory and vessel stabilizing effects that may last longer compared to classical anti-VEGF agents. This article is a systematic review that aims to assess the efficacy and safety of faricimab in neovascular age related macular degeneration (nAMD) in naïve and non-naïve patients, previously treated with intra-vitreal anti-VEGF.

Materials and Methods

A comprehensive search was conducted on PubMed and Web of Science by the mesh terms “faricimab” AND “age related macular degeneration” or “wet AMD” or “neovascular AMD”. All articles in English language for which full text could be obtained were included. An addition hand search was performed in the references of the relevant reviews on the topic. Editorials, commentaries, meeting abstracts, letters and book chapters were excluded. The strategy of research followed PICOS acronyms as recommended by PRISMA guidelines [11]; P: patients with wet AMD, naïve or previously treated with other anti-VEGF agents; I: intravitreal faricimab, 6 mg/0.05 mL, at least one dose; C: comparison to a match cohort of intravitreal anti-VEGF only treated nAMD patients was analysed when available; O: improvement in visual acuity (VA) and/or central macular thickness, measured by optical coherence tomography (OCT); S: any types of clinical studies were included in the review.

The protocol of intravitreal injections, doses, number of patients, follow-up time and side-effects were also documented. The research was carried out by 2 researchers. Any disagreement was solved by discussion.

Risk of bias

Although the studies included in the review were comparable regarding the protocol of research and measured outcomes, we encountered differences that may be possible sources of bias. The anatomical outcomes were measured by all authors in terms of central retinal thickness (CRT) or central subfield thickness (CST), while some studies evaluated also the changes in central choroidal thickness (CCT) or the height of intraretinal/subretinal fluid, by optical coherence tomography (OCT). Some studies included naïve nAMD patients, and aimed to comparatively assess the outcomes after faricimab (Vabysmo™, Roche, 6 mg/0.05 mL) and anti-VEGF agents, others investigated the effects of faricimab in refractory nAMD patients or with sub-optimal response to previous anti-VEGF therapy. For these reasons, the studies included in the systematic review were analysed only qualitatively.

Results and Discussion

The initial search returned a total of 138 articles. After duplication removal and application of the inclusion and exclusion criteria, a number of 16 papers, were included in the qualitative analysis. The flowchart of the research strategy is presented in Figure 1.

The studies included in the review were published between 2020 and 2023, and reported data on a total of 2970 patients with nAMD, with a mean follow-up period of 24.27 ± 13.3 weeks (Tabel I).

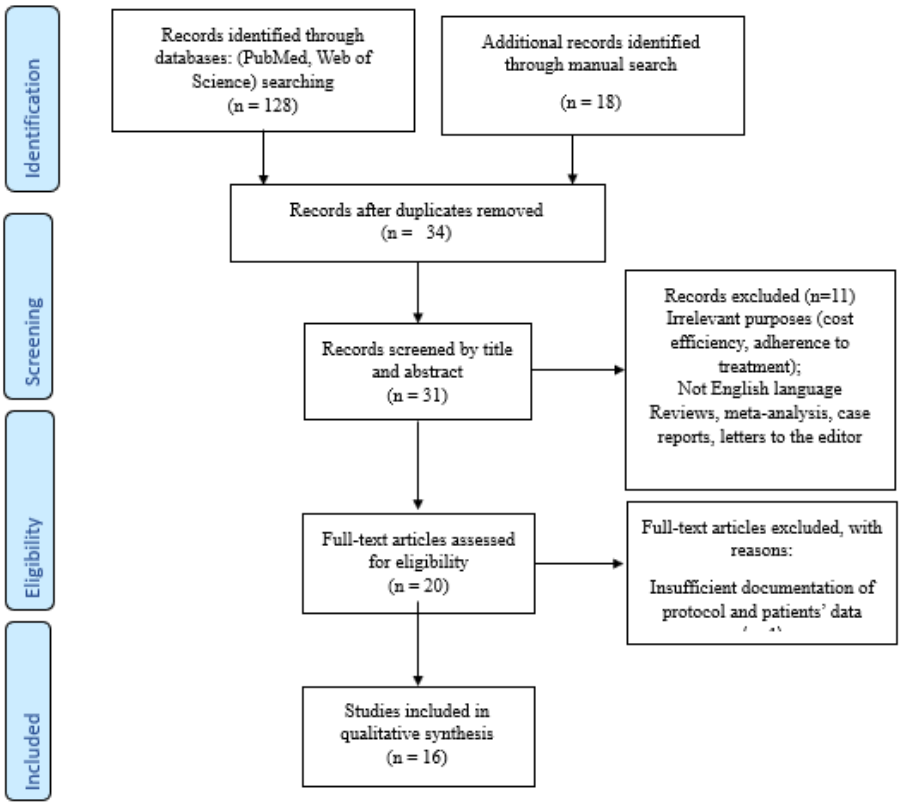

Figure 1.
PRISMA flowchart for the studies included in the review

Table I
General description of the articles included in the present review

Author, year	Study, protocol	Patients	Number	Follow-up (weeks)	BCVA	CCT	CST	Mean interval between injections* (weeks)	Others	Side effects
Khanani AM, 2020 [12]	STAIRWAY phase 2 trial, IVF *vs*. IVR	Naïve nAMD, 3 study arms: IVR q4w; IVF q12w; IVFq16w	76 (16, 29, 31)	52	No difference between study arms	No info	↓ No difference between study arms	No info	No info	No differences between study arms
Sahni J, 2020 [4]	AVENUE phase 2 trial IVF *vs*. IVR	Naïve nAMD (5 study arms: Rq4w; Fq4w; Fq8w; Rq4w until 8w, then Fq4w)	365 (68, 47, 42, 47, 69)	36	No difference between study arms	No info	↓ No difference between study arms	No info	No info	No difference between study arms
Heier JS, 2022 [13]	TENAYA/ LUCERNE phase 3 trials: IVF up to 16W *vs*. IVA q8W	Naïve nAMD	1329 (665 IVF; 364 IVA)	48	No differences in BCVA change (5.8 *vs*. 5.1 letters)	No info	↓ No difference between study arms	No info	Similar NEI VFQ-25 composite score	No difference between study arms

Author, year	Study, protocol	Patients	Number	Follow-up (weeks)	BCVA	CCT	CST	Mean interval between injections* (weeks)	Others	Side effects
Hikichi T, 2023 [14]	TAE	Switch from IVA	48	24	No change	No info	↓ (272 ± 14 µm *vs*. 372 ± 20 µm)	↑ (10.45 ± 0.44 weeks *vs*. 6.72 ± 0.34)	↑ MacTSQ at 6 months (56.8 ± 1.8 *vs*. 49.5 ± 1.9)	none
Inoda S, 2023 [15]	IVF 6 mg/ 0.05 mL, 1 dose	nAMD treated with IVA/IVBr, > 6 months before	75 (80 eyes); 25 IVA; 50 IVBr	No info	No change (0.34 ± 0.37 *vs*. 0.36 ± 0.40)	↓ (179 ± 97 to 189 ± 98 µm ($p < 0.0001$)	No change (242 ± 72 to 242 ± 82 µm) ($p = 0.99$)	No info	No info	none
Matsumoto H, 2023 [16]	3 monthly IVF	Naïve nAMD	38 (40 eyes)	16	↓ (0.22 ± 0.36 *vs*. 0.33 ± 0.41)	↓ (192 ± 89 µm *vs*. 214 ± 98 µm)	↓ (173 ± 48 µm *vs*. 278 ± 116 µm)	No info	No info	Vitritis: 1 case (2.5%)
Stanga PE, 2023 [17]	1 monthly IVF	Naïve and non-naïve nAMD	11 (3 naives; 8 non-naives)	4	↓ (0.387 ± 0.54 *vs*. 0.612 ± 0.75)	No info	↓ (256.16 ± 12.98 µm *vs*. 536.04 ± 36.15 µm)	No info	75% total remission of SRF;66% remission of IRF;↓ PED	No info
Maruyama-Inoue M, 2023 [10]	3 monthly IVF *vs*. IVBr	Naïve nAMD	90 (92 eyes); 49 (50 eyes) IVF; 41 (42 eyes) IVB group	20	No change (0.28 ± 0.32 *vs*. 0.30 ± 0.36)	No difference (194 ± 95 µm *vs*. 167 ± 83 µm)	No difference (226 ± 94 µm *vs*. 253 ± 124 µm)	No info	No info	IVF: none; IVBr: IOI 1(2.4%), RPE tears 2(4.8%);
Szigiato, A, 2023 [18]	3 monthly IVF	nAMD with sub-optimal response to other ant-VEGF	106 (126 eyes)	24.3 ± 5.2	No change	No info	↓ (249.8 ± 58.6 µm *vs*. 266.8 ± 64.7)	No info	PED: ↓ (206.9 ± 130.0 µm *vs*. 249.6 ± 179.0)	ocular inflammation: 1 case (0.94%)
Kataoka K, 2023 [19]	4 monthly IVF, followed by IVF at a minimum of 2-month	Refractory nAMD treated with IVA	124 (130 eyes) at baseline; 53 eyes (40.8%) continued on IVF at 6 months;	up to 24	No change	No info	No change	↑ (8.7 ± 1.7 weeks *vs*. 4.4 ± 0.5)	No info	ocular inflammation: 1case (0.7%)
Kishi M, 2023 [20]	IVF, on TAE regimen	Refractory nAMD treated with IVA	55 (55 eyes)	16	No change	No change	↓	↑ (7.5 ± 2.3 *vs*. 5.9 ± 1.5)	↓IRF and SRF	RPE tear: 1 case (1.8%)

Author, year	Study, protocol	Patients	Number	Follow-up (weeks)	BCVA	CCT	CST	Mean interval between injections* (weeks)	Others	Side effects
Cheng, AM, 2023 [23]	Monthly IVF	refractory nAMD, treated with IVA/ IVB/IVR	11 (13 eyes)	13.6 ± 4.8	No change (0.59 ± 0.45 *vs.* 0.58 ± 0.45)	No info	↓ (318µm *vs.* 342µm)	No info	↓IRF/SRF	none
Leung EH, 2023 [22]	3 monthly IVF, followed by TAE regimen	Non-naïve nAMD (mixed criteria)	190 eyes	34.88 ± 8.2	↑ (0.33 ± 0.32 *vs.* 0.27 ± 0.32)	No info	↓ (287 ± 71 µm *vs.* 312 ± 87 µm)	↑ (7.64 ± 6.2 *vs.* 5.16 ± 2.0 IVR and 5.57 ± 3.6 IVA)	No info	RPE tear: 4 cases (2%); subretinal haemorrhages 3 cases (1.6%)
Rush RB, 2022 [23]	3 monthly IVF *vs.* IVA	Non-naïve nAMD	28 (IVF) 27 (IVA)	16	↑ Gain 2 or more lines of VA: 35.7% (IVF) *vs.* 7.4% (IVA)	No info	↓ (328.7 *vs.* 379.4)	No info	No info	none
Khanani AM, 2023 [24]	TRUCKEE study, real world	Naive and non-naïve nAMD	335 (376 eyes)	24	↑ (+1.1 letters (p=0.035) at 1 months; + 3.4 letters (p = 0.03) after 3 IVF)	No info	↓ (-31.3 µm at 1 months; -43.4 µm after 3 IVF)	No info	Resolution of IRF, SRF, PED: 17.8%; 36.6%; 11.1% at 1 month; 21.4%; 20.8; 14.9 at 3 months	Infectious endophthalmitis: 1 case (0.54%); Uveitis: 1 case; (0.54%)
Mukai R, 2023 [25]	multicentric	Naïve nAMD	61 (63 eyes)	12	↑ (0.32 ± 0.43 *vs.* 0.40 ± 0.42)	No info	↓ (175 ± 91 µm *vs.* 357 ± 165 µm)	No info	Dry macula 82% at 3 months	RPE tear: 2 cases (3.1%)

Footnote: BCVA: best corrected visual acuity; CST: central subfield thickness; CCT: central choroidal thickness; IVF: intravitreal faricimab; IVA: intravitreal aflibercept; IVB: intravitreal bevacizumab; IVBr: intravitreal brolucizumab; *: after initial loading of 4 injections monthly. RPE: retinal pigmented epithelium; TAE: treat and extend regimen;

IVF in naïve patients with nAMD

Six studies reported data on naïve nAMD treated with IVF [4, 10, 12, 13, 16, 25], either as single arm [16, 25], or as multiple arms studies [4, 10, 12, 13], proving data supporting non-inferiority of IVF to other anti-VEGF, such as aflibercept, ranibizumab and brolucizumab, in terms of functional and anatomic outcomes. Moreover, Heier *et al*. [13], in the phase 3 study TENAYA and LUCERNE, found that the results could be maintained with up to 16 weeks interval between injections, after a loading period of 4 injections monthly, which would be a significant decreased burden on the patients with nAMD.

AVENUE study [4] is a phase 2 multicentric double-masked randomized study including 365 naïve nAMD patients, with a follow-up period of 36 weeks, that compared the outcomes of 5 study arms: ranibizumab (Lucentis®, Genentech/Roche, 0.5 mg in 0.05 mL), 0.5 mg every 4 weeks; faricimab (Vabysmo™, Roche, 6 mg/0.05 mL), 1.5 mg every 4 weeks, faricimab, 6.0 mg every 4 weeks, faricimab, 6.0 mg every 4 weeks until week 12, followed by faricimab, 6.0 mg every 8 weeks and ranibizumab, 0.5 mg every 4 weeks until week 8, then faricimab, 6.0 mg every 4 weeks. The results found no statistical differences between the study arms, regarding anatomical and functional outcomes, as well as similar adverse effects. While the study failed to find a superior visual outcome provided by faricimab over ranibizumab, the results showed the potential prolonged effect of faricimab, which could allow the increase of the mean interval between injections. Similarly, the STAIRWAYS study [12]

showed comparable anatomical and functional outcomes when compared intravitreal ranibizumab every 4 weeks with intravitreal faricimab every 12 weeks or every 6 weeks.

Phase 3 studies TENAYA and LUCERNE [13] involved 1329 naïve nAMD patients from 271 centres world-wide, that were double blind assigned to either Faricimab (Vabysmo™, Roche, 6 mg/0.05 mL), up to 16 weeks, after a loading period of 4 monthly injections or Aflibercept (Eylea®, Bayer, 2 mg/0.05 mL) up to 8 weeks, after a loading period of 3 monthly intravitreal injections. The primary end-point, measured as the mean change in BCVA at 40, 44 and 48 weeks showed not statistical different results between the two study arms (+ 5.8 - 6.6 *vs*. + 5.1 - 6.6, Early Treatment Diabetic Retinopathy Study (ETDRS) letters). As secondary outcomes, 80% of faricimab-treated patients were on ≥ 12-week dosing intervals, at week 48. Moreover, 44.9% (TENAYA) and 45.7% (LUCERNE) of patients were on 16-week dosing intervals [13].

Maruyama Inoue *et al*. [10] evaluated comparatively the outcomes of faricimab (Vabysmo™, Roche, 6 mg/0.05 mL) and brolucizumab (Beovu®, Novartis, 6 mg/0.05 mL), after 3 monthly intravitreal injections, on 90 patients and found similar results. No differences were observed either in BCVA mean gain or decrease of CRT. As serious side-effects, the study found none in the IVF group, while in the IVR group there were 1 case of intraocular inflammation (2.4%) and 2 cases of RPE tear (4.8%). However, Mukai *et al*. [25], in a study on 61 patients treated with IVF, found RPE tear in 3.1% of cases. These data suggest that expected side-effects after IVF are comparable with those already documented in anti-VEGF treatment.

IVF as switch therapy after IVA /IVB

In the present systematic review, seven studies evaluated the effects of IVF therapy in non-naïve patients, refractory or with sub-optimal response to classical anti-VEGF [14, 18-23], while 2 were real-life studies including both naïve and non-naïve nAMD cases [17, 24].

Two out of seven studies (28.5%) found that switching from other anti-VEGF to faricimab in patients with sub-optimal response resulted in improvements of vision and anatomic outcomes [22, 23]. However, most researches (4 studies, 57%) found insignificant changes in BCVA during the follow-up period, but certain anatomical improvements in the IVF group, such as significant decrease in CCT [15] or CST and intra and subretinal fluid height [18, 20, 21]. Only one study found not statistical differences between IVF and IVA both in terms of visual gain and anatomical improvements [19]. In a study of Kataoka *et al*. [19], on 120 patients with refractory nAMD previously treated with aflibercept, the switch to IVF was done by 4 monthly injections, followed by up to 2 monthly repeated doses. Although after the first month, CRT and SFCT significantly decreased, the difference was lost at 6 months evaluation. Moreover, only 53 eyes (40.8%) continued the treatment with IVF at 6 months, while 77 eyes (59.2%) discontinued IVF, the main reason being increased exudation (71 cases, 57.2%), loss of follow-up (3 cases 2.4%), ocular inflammation (1 case, 0.7%). However, the mean interval between injections were higher in IVF *vs*. IVA group (8.7 ± 1.7 weeks *vs*. 4.4 ± 0.5), suggesting a better control of the disease by using combined anti-Ang2/Tie and anti-VEGF therapy [19].

Szigiato *et al*. [18] performed a prospective study on 106 non-naïve nAMD patients with (126 eyes), most of whom were treated with aflibercept (87%), with a mean treatment interval with any anti-VEGF was 5.6 ± 1.6 weeks before switching. After 3 monthly IVF, the visual acuity remained stable in the study group, but with significant decrease of CST and PED [18]. The switch was well tolerated, with only one case of intraocular inflammation (0.94%). However, the authors could not evaluate the persistence of the IVF effects due to the limited follow-up period.

TRUCKEE study [24] involved 335 naïve and non-naïve patients, who completed at least one follow-up visit. Faricimab proved to be efficient in improving anatomical results, with decreased CRT, subretinal and intraretinal fluid in both naïve patients and those previously treated with any other anti-VEGF. However, visual function was improved more in the naïve group compared to aflibercept treated patients (+ 4.9 letters *vs*. + 0.7 letters) at 1 month follow-up. Further continuation of IVF with a loading dose seems to be beneficial in real world patients, according to the TRUCKEE study [24], with mean vision gain from baseline of + 3.4 letters, significantly higher in naïve nAMD patients *vs*. those switched from other anti-VEGF (+ 8.1 letters *vs*. + 2.7 letters).

Safety of intravitreal faricimab (IVF)

In the reviewed studies, the incidence of systemic serious effects, including APTC events (0.9 - 1.2%), was low, and they were not considered related to the treatment. The serious ocular side-effects were few, varying from none [10] to 3.1% [25] and comparable to those encountered in classical anti-VEGF therapy The ocular complications included transient raised intraocular pressure (0 - 2.4%), ocular inflammation and vitritis (1.5 - 3.1%), that could be managed conservatory, without causing a further decreased in vision. Schönbach *et al*. [26] reported a case of postoperative hypotony and suprachoroidal haemorrhage, in a patient with no significant risk factors, which resorbed with medical therapy after 2 months. RPE tears were reported in 1 - 2% in the reviewed studies, at up to 48 weeks after treatment with faricimab, not exceeding the previous data regarding other anti-VEGF agents. The main risk factors for RPE are considered large PEDs, with microrips, exceeding 400 μm height [20, 27] and with less than 50% component of macular neovascularization [28]. In these patients, either

faricimab or mono anti-VEGF therapy may increase mechanical stress on RPE monolayer, due to contraction of the choroidal neovascular membrane.

The pathology of nAMD is multifactorial and still incompletely understood. Along with the VEGF, a significant role in the vascular stability is played by angiopoietin-tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (Ang-Tie) pathway. While Ang-1 promotes vascular stability and endothelial cell survival, Ang2 acts as a competitive antagonist, inhibiting phosphorylation and leading to increase vascular permeability and inflammation, [29, 30]. Oxidative stress leads to local chronic inflammation, as a response to damages tissue and increased influx of inflammatory cytokines, complement system activation and endothelial dysfunction [30-34]. In hypoxia and inflammation, Ang2 is freed from Weibel-Palade bodies of the endothelial cells and acts by an autocrine manner, by blocking Tie 2 and promoting vascular destabilization and apoptosis of the endothelial cells, disruptions of the basal membrane and pericytes loss [35-38].

Faricimab is a 126 kDa bispecific antibody which independently binds Ang2 and VEGF [4, 35]. Thus, it acts on 2 different pathological pathways. This dual action might explain the prolonged effects of suppression the neovascular membrane growth observed in the reviewed clinical studies. Moreover, due to its anti-inflammatory effect, it may be associated with less subretinal fibrosis [39, 40]. Inoda *et al*. [15] found that dual Ang2/VEGF-A inhibition potentiates choroidal vascular remodeling, which might give better results for Asian patients with nAMD, especially those associated with the pachychoroid phenotype. However, they did not find superior BCVA or improvements in other anatomical results with IFV in patients previously treated with intravitreal aflibercept of brolucizumab [15].

Maruyama-Inoue *et al*. [10] found in a real-life study with a 4 months follow-up that the improvements in VA and decrease of CCT and CMT were more significant in IVBr *vs*. IVF group at 1 month, but the outcomes were not statistically different at 4 months follow-up. One explanation might be the smaller molecule of brolucizumab compared to faricimab (26 *vs*. 146 kDa), which may diffuse earlier into retinal tissue. One the other hand, at a similar dose of 6 mg/ 0.05 mL, one might assume that there are more molecules of brolucizumab *vs*. faricimab to bind with VEGF-A specific receptors, making the first more effective due to higher bioavailability [10]. However, the supplementary action of blocking of Ang2 receptors of faricimab may be responsible for the longer time effects, as shown by TENAYA and LUCERNE studies [10, 13, 41, 42].

Disease control offered by dual Ang2 and VEGF pathway inhibition with faricimab may improve outcomes in patients, by allowing extending the interval between scheduled visits. This may improve the patients quality of life, but also decrease the economic burden and overcrowding in the treating facilities [43-46]. Kataoka *et al*. [19] found that faricimab may be useful in up to 41% of patients with refractory nAMD, the main advantage being obtaining persistent results, which allow increasing the time between injections. However, no predictive factors could be identified between the patients that responded and those who did not improve with faricimab. Further studies, involving local cytokines and possible predictive biomarkers are necessary to better understand the phisiopathological mechanisms in nAMD.

Conclusions

Combined intravitreal anti-VEGF and anti-Ang2/tie therapy is safe and efficient in patients with nAMD, and seems to have a longer effect in time combined to intravitreal anti-VEGF alone. Although in long term, the anatomical and functional results do not differ significantly from standard anti-VEGF therapy, the possibility of increasing the time between scheduled visits may ease the burden on the patients, allowing them to have a better quality of life.

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Conflict of interest

The authors declare no conflict of interest.

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